UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/340,283	06/25/99	MESSING	R GALO-007/01U

EXAMINER	
SARWAN, R	PAPER NUMBER

HM12/0324

PATENT GROUP
COOLEY GODWARD LLP
FIVE PALO ALTO SQUARE
3000 EL CAMINO REAL
PALO ALTO CA 94306-2155

ART UNIT: 1632

DATE MAILED: 03/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/340,283	Messing et al
Examiner	**Group Art Unit**
Ram Shukla	1632

☒ Responsive to communication(s) filed on *Feb 29, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-28* is/are pending in the applicat

Of the above, claim(s) *1-9 and 11-28* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. Amendment filed 2-29-00 (paper # 6) has been entered.

2. Applicant's election without traverse of the invention of group II, claim 10 in Paper No. 6 is acknowledged.

3. Claims 1-9 and 11-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

4. Claim 10 is under consideration.

Priority

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) over provisional applications 60/09755, filed 7-6-1998 and 60/125995, filed 3-24-1999 is acknowledged.

Oath/Declaration

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

the Serial Number of the application is omitted. It is noted that in place of the serial number of the application, Attorney's docket number is provided.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method wherein the PKC-epsilon modulatory activity is tested in vitro in cell culture and then its anti-anxiety activity is tested in a transgenic mouse model of anxiety,

does not reasonably provide enablement for method wherein the activity of a compound is first tested for modulating the activity of PKC-EPSILON by any and all methods and then it's activity is tested for anti anxiety effects in any and all subjects. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and practice the invention commensurate in scope with these claims. .

Claim 10 is drawn to a method of screening for anxiety modulatory compounds, comprising : first determining the PCK-epsilon modulatory activities of a compound and then administering it to a subject to determine it said compound modulates anxiety.

While determining whether a specification is enabling for a claimed invention, one considers whether the specification itself or prior art discloses sufficient guidance and ample exemplification and whether there is sufficient evidence that an artisan of skill would have been able to make and use the invention as claimed without undue experimentation. In the instant case, the invention recites a method of identifying compounds that modulate anxiety by first determining whether a compound modulates PKC-EPSILON activity and if it does, test its anxiety modulatory activity in a subject. The specification is not enabling for the claimed method because the specification has not disclosed sufficient guidance to make and practice the claimed method in a subject and an artisan of skill would have required undue experimentation to practice the claimed method.

First, the issues is, what is the method of testing the PCK-EPSILON modulatory activities of a compound, would it be determined in in vitro system or in in vivo system? Specification on page 29-32 (starting on lines 25-30 on page 29 continued till page 36) discloses assays used for identifying compounds that modify the activity of PKC-EPSILON and that such compounds may be inhibitors or activators of PKC-EPSILON activity and that cells expressing PKC-EPSILON or purified enzyme preparations or enzyme immobilized on solid support may be used for screening such compounds. While the methods of assaying PKC-EPSILON's activity by compounds is well known in the art, the question is: can the results obtained in in vitro systems be extrapolated to in vivo systems or can an effect on the activity of PCK-EPSILON in vitro be reproduced in vivo when the same compound is given to an animal in vivo? It is well known in the prior art that

effects of compounds on a purified preparation of an enzyme may not be necessarily reproduced when the same assay is carried out in a cell culture system. Likewise, the effects of a compound in a cell culture system may not be reproducible when the same compound is administered to an animal because the milieu of growth factors that regulate the growth and differentiation of an cell in vitro in cell culture may be very different that those in vivo. Specification on page 26 summarize the characteristics of a transgenic mouse they have produced wherein both the alleles of PKC-EPSILON gene have been inactivated. The specification asserts that while this mouse has a normal body weight, eating, drinking and normal gross locomotor behavior, it demonstrated differences when open-field activity, exploration of a novel object, and elevated plus maze performances were tested. Some of the studies that characterized the PKC-EPSILON null mouse are described in figures 1-21. It is noted that figures 5 and 7-9 disclose data from both male and female mice and there are clear differences in the two sexes of mice. For example, as disclosed in figure 5, there was no difference in body of mutant male or female mice, when the body weight was compared with the same sex control, however, when body weight of male and female mice was compared there was significant difference between both wild type and mutant mice. It is not clear what is meant by these observations because a significant weight difference between wild type male and female mice will negate the change in the weight of mutant male Vs female mice. Likewise, figure 9 compares the performance of wild type and mutant male and female mice in elevated pus maze test. In this test, while the male mutant rats compared to male wild type mice showed higher scores, however, the differences between wild type and female mutant mice were not significant, if any thing they were reverse of male, i.e. wild type had higher values compared to mutant. Rest of the figures do not indicate whether the tests or studies were done in male or female mice. If one anticipates that these studies would have been done in male mice because effect of mutation was more consistent, then one can also infer that mutant female mice of the invention can not be reliably used in the study. Next, can the activity of a compound be tested for PKC-EPSILON modulation in the mutant mouse disclosed in the application. Since the mouse is not expressing this isozyme of PKC, it can not be used for testing the activity of PKC-EPSILON in vivo. In summary, the specification does not provide sufficient disclosure about the in vivo methods of testing compounds that would have PKC-EPSILON modulatory activity.

Next, the question is: what is a subject, who can be used for determining efficacy of a compound in modulating the state of anxiety? The specification, as filed does not explicitly define what a subject will be? However, conventionally it is interpreted as a test animal. Then the question is can any animal be a subject for determining efficacy of a compound in modulating the activity of anxiety. The specification as filed is not enabling for using any animal as a subject in practicing the claimed method because an artisan of skill would not know whether any animal can be used as a model for anxiety and whether the PKC-epsilon mutant mouse is an accepted model for anxiety. As stated earlier while the male transgenic mice that are PKC-EPSILON null mutant have characteristic open-field activity, exploration of a novel object, and elevated plus maze performances that is similar to the animal models of anxiety, such as corticotropin releasing factor transgenic mice (Stenzel-Poore MP et al. 14:2579-2584, 1994). It is not clear from the disclosure in the specification whether female mutant mice (null for PKC-epsilon) have anxiety related characterisitics. Therefore, the specification is not enabling for the use of any animal in the claimed method because, for example, as discussed above, female mice that are null for PKC-EPSILON do not have the same characteristics as the male mice. Additionally, Rogers et al (Rogers DC. Behavioral Brain Research 105: 207-217, 1999) teach that there are marked differences in the behavior phenotype of six inbred strains of mice, which would indicate that any mice may not be used for comparing phenotypes of mice (see abstract).

In conclusion, the specification is not enabling for the claimed method wherein the activity of a compound is first tested for modulating the activity of PKC-EPSILON and then it's activity is tested for anti anxiety effects in a subject because the specification does not provide sufficient guidance as to how an artisan of skill would have tested the PKC epsilon modulatory activity in any and all assay systems and wherein the anti-anxiety activity of the compound would have been tested in any and all subjects. Therefore, limitation of the scope of the claimed method to a method wherein the PKC-EPSILON modulatory activity is tested in vitro in cell culture and then its ant-anxiety activity is tested in a transgenic mouse model of anxiety.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how is the modulation of PKC-EPSILON activity by a test compound monitored, is the modulation of PKC-EPSILON tested in vitro or in vivo, how is it determined that a test compound modulates the symptoms of anxiety or what are the symptoms of anxiety that are monitored.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is vague and indefinite because it is not clear what is meant by a subject, for example is a subject an animal, a human etc. For examination purposes, a subject is interpreted as a test animal.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salzman et al (Salzman C et al. Harv Rev Psychiatry. 1: 197-206, 1993) in view of Berg et al (Berg KA et al. Molecular Pharmacology 45:826-836, 1994) and Stenzel-Poore et al (Stenzel-Poore MP et al. 14:2579-2584, 1994).

The invention of claim 10 has been summarized in para 8.

Salzman et al teach review the state of the art of the neurologic basis of anxiety. They add that alteration of the influx of chloride ions within benzodiazepine-GABA receptor complex is associated with the development of anxiety and that the clinical effects of benzodiazepines are mediated via this receptor complex. Subtypes of benzodiazepine receptors and endogenous benzodiazepine ligands have also been identified and their role in pathogenesis of anxiety has been suggested. Salzman et al state "In the future, drugs that affect these varying benzodiazepine functions may play a role in the treatment of anxiety". Salzman et al further teach that drugs affecting the noradrenergic beta receptor and 5-hydoxytryptamine (serotonin) receptors have anxiolytic properties (see abstract). Salzman et al do not teach a method of identifying compounds that modulate anxiety by monitoring the effect of PKC epsilon modulators on anxiety in a subject.

Berg et al teach the 5-HT receptors regulate signal transduction in a neuronal cell line by Protein kinase c dependent mechanism and calcium/calmodulin dependent mechanisms. Berg et al show that PKC-epsilon remains associated with the membrane fraction even in the when cells are treated with PMA to deplete PKC and that treatment with 5-HT in PKC depleted cells produced signal transduction and that this signal transduction was reduced when treated with calmodulin antagonists or calcium chelators (see abstract).

Stenzel-Poore et al teach a genetic model of anxiogenic behavior wherein a transgenic mice that overproduces corticotropin-releasing factor has the characteristics of anxiety as shown by anxiogenic behavior in locomotor activity tests in novel environment and an elevated plus-maze test. They further teach that administration of CRF receptor antagonist reverses the exploratory behavior of the mice in response to environmental stress and suggest that the CRF transgenic mice is well suited for testing neurogenic hypotheses in the pathogenesis of human psychopathology.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to have modified the method of Berg et al and tested the effect of a compound, that modulated the activity of GABA receptors or 5-HT receptors, on PKC-EPSILON activity in vitro in cell culture

and then tested the effect of compounds that affected the activities of GABA or 5-HT receptors and of PKC-EPSILON activity in the transgenic animal model of anxiety, such as in CRF transgenic mouse. An artisan would have been motivated to screen such compounds, that affect neurotransmitter activity, for PKC-EPSILON modulatory and anxiolytic modulatory activity because such compounds can be as drugs for treating anxiety as suggested by Salzman et al.

13. Claim 10 is not allowed.

14. The article by Hodge et al (Hodge CW et al. Nature Neuroscience 2:997-1002, 1999) is made of record. This article teaches a transgenic mouse which lacks both the alleles of PKC-epsilon and is sensitive to GABA receptor modulators and develops the characteristics of anxiety.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.

Jasemine Chambers

JASEMINE CHAMBERS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600